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AN INVESTIGATION ON THE CENTRAL EFFECTS OF HARMINE, HARMALINE AND RELATED β-CARBOLINES

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Summary—The behavioural and EEG effects of harmine, harmaline and 5 related β-carbolines were studied in rats and rabbits bearing chronically implanted electrodes in various cortical and subcortical areas. Based on the results obtained, the 7 derivatives can be divided into 3 groups. The first group includes harmine and harmaline, which caused excitation, tremors, and ataxia both in the rat and in the rabbit. The modifications of the cerebral electrical activity during the tremors consisted of an increase in frequency and in voltage, observed in the cortical leads. Harmol, tetrahydro-harmane and 3-methyl-harmane had a different toxic effect, consisting of a depressive syndrome, which can extend to complete paralysis in the rat. Harmane and nor-harmane produced, at low doses, a motor depression having a catatonic component; higher doses led to clonic and tonic–clonic type convulsions; tremors were never observed. In the rabbit, but not in the rat, L-DOPA was effective in antagonizing the tremors and the other toxic symptoms caused by the two drugs. These results suggest that the tremors induced by harmine and harmaline may be caused by an effect on the extrapyramidal dopaminergic system.

THE FIRST systematic study of the effects of harmine, harmaline and of other β-carbolines on laboratory animals was carried out by GUNN *et al.* (1930, 1931, 1935). Tremors, convulsions and excitation characterized the toxic syndrome induced by harmine and harmaline. This has been confirmed by other investigators (CHEN and CHEN, 1939). Later on, an anti-monoamine oxidase effect was described for both alkaloids (PLETSCHER *et al.*, 1959). Other authors have, in particular, examined the effects of harmine on the central nervous system. GERSHON and LANG (1962) reported a state of 'anxiety' and excitation in the dog. HIMWICH *et al.* (1959) studied the effect of the alkaloid on the cerebral electrical activity of the rabbit, describing EEG activation after 5 mg/kg. The tremorigenic effect of harmine in mice was analyzed by HARA and KAWAMORI (1954). These authors noticed that the tremors disappeared after ablation of either the cerebral cortex or the striatum. On the basis of these findings they suggested that the drug affected the extrapyramidal system. Recent biochemical studies seem to uphold this theory; according to POIRIER *et al.* (1968), harmaline has a specific effect on brain dopamine and hinders both its synthesis from L-DOPA and its conversion into homovanillic acid. Therefore, the tremor elicited by these alkaloids could be deemed analogous to the syndrome observed in mammals (monkey) and man with lesions of the extrapyramidal system.

As to the other derivatives with a β-carboline structure, literature dealing with pharmacological findings is scarce. GUNN and MACKEITH (1931) calls attention to the fact that harmol causes a paralysis instead of the excitation observed with the methoxylated

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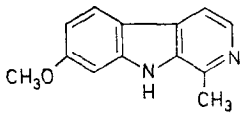
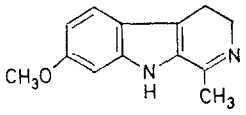
derivatives. The pharmacological properties of harmane were studied by SIGG *et al.* (1964); they described a convulsant effect.

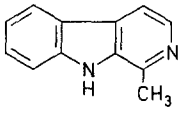
In the present work the effects of harmine, harmaline, and of five other β-carbolines (see Table) were studied in animals with chronically implanted electrodes. The scope of



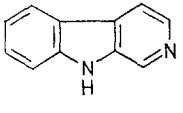
Harmine



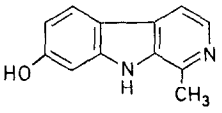
Harmaline



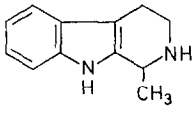
Harmane



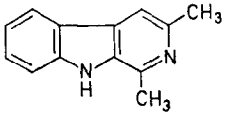
Nor-Harmane



Harmol



Tetrahydro-Harmane



3-Methyl-Harmane

TABLE. CHEMICAL STRUCTURES OF THE 7 COMPOUNDS STUDIED.

our investigations was that of determining any change of cerebral electrical activity that could be related to the motor alterations and, in particular, to the tremors which seem to be a characteristic effect of some of these compounds. The antagonism of some drugs to the toxic syndrome provoked by harmine and harmaline has also been studied.

METHODS

In preliminary experiments, the drugs were administered to rats and rabbits to observe the toxic effect and determine the lethal dose. A total of 40 rats and 22 rabbits were used for this purpose. Other preliminary experiments dealt with the action of the compounds on the cerebral electrical activity of rabbits in which electrodes were acutely implanted under ether anaesthesia. Arterial pressure was recorded from a cannula inserted in the femoral artery and connected to a strain gauge transducer. All the wounds were infiltrated with procaine. The animals were then immobilized with gallamine (5 mg/kg) and placed under artificial respiration.

Experiments were then performed on rats and rabbits bearing chronically implanted

electrodes in various cortical and subcortical areas. Histological examinations were performed at the end of the experiments to ascertain the position of the deep electrodes. These animals were placed in a shielded box (1m × 1m) and were connected to the EEG apparatus with long wires allowing freedom of movement. To analyse the EEG recordings a two-channel frequency analyser (Faraday Electronic Instruments) was employed.

Besides observing the spontaneously displayed behaviour of the animal, the following methods were used to evaluate other motor deficits occurring in the course of intoxication. The presence of catatonia in the rat was assessed by placing one foreleg on a 7 cm high wood cube. In the rabbit, the intensity and frequency of the tremors was measured by introducing bipolar needle-electrodes in various muscles (foreleg, hindleg, neck). The abnormal postures assumed by the animals under the effect of the drugs were often photographed.

All the substances were dissolved in water; the doses are expressed as the weight of the free base. Unless otherwise stated, the rats received the drugs intraperitoneally, while the rabbits were injected intravenously. In the experiments carried out in the animals with chronically implanted electrodes, at least 3 days were allowed to elapse between subsequent drug treatment.

RESULTS

I. Rat

Harmine, harmaline. Preliminary trials were carried out in rats to determine the dose capable of inducing the typical symptoms of intoxication (tremors, excitations). In these trials it was found that, up to 30 mg/kg, neither harmine nor harmaline provoked the death of the animals. Experimentation was then begun using animals bearing chronically implanted electrodes. Six rats were used, for a total of 22 experiments; the dose administered varied from 2 to 20 mg/kg. No significant differences in potency between the two drugs were noted. Rats receiving harmine or harmaline in doses of 5–10 mg/kg, after a short period of latency (5 min) showed an increase in spontaneous activity with tremors and an unsteady gait. Tremors, however, were not evident when the animals were not moving. After 15–20 mg/kg, the tremor appeared almost immediately; it was independent of the spontaneous movements and was accompanied by arching of the back and stiffening of the legs. In some cases the animals fell on their sides and had clonic convulsions. The continuous tremors lasted for about 10 min and then progressively diminished, leading to the less severe syndrome described for the lower doses.

The modifications of the cerebral electrical activity during the tremors consisted of an increase in frequency and voltage, observed in the cortical anterior leads; this increase in frequency is well evident in the frequency analysis diagram (Fig. 1). This EEG modification was clearly dissociated from the artifacts due to the increased muscular activity, for it was present in the records even during the periods when animals did not have tremors.

The effect of L-DOPA on the toxic syndrome produced by harmine was studied in 14 rats. Groups of 4 animals were treated respectively with 10 and 20 mg/kg of harmine and 20 of harmaline; once the tremors were fully developed they were injected with dosages of L-DOPA varying from 10 to 50 mg/kg. No appreciable attenuation of the toxic syndrome was observed. Two animals treated with 20 mg/kg of either harmine or harmaline received L-DOPA intravenously through a needle inserted into the tail vein; also in this case the drug (50 and 100 mg/kg) did not modify the tremors and the other symptoms of intoxication. Along with the above described experiments, some preliminary trials were undertaken to study the effect of 5-hydroxytryptophan (5-HTP) on the toxic syndrome produced by

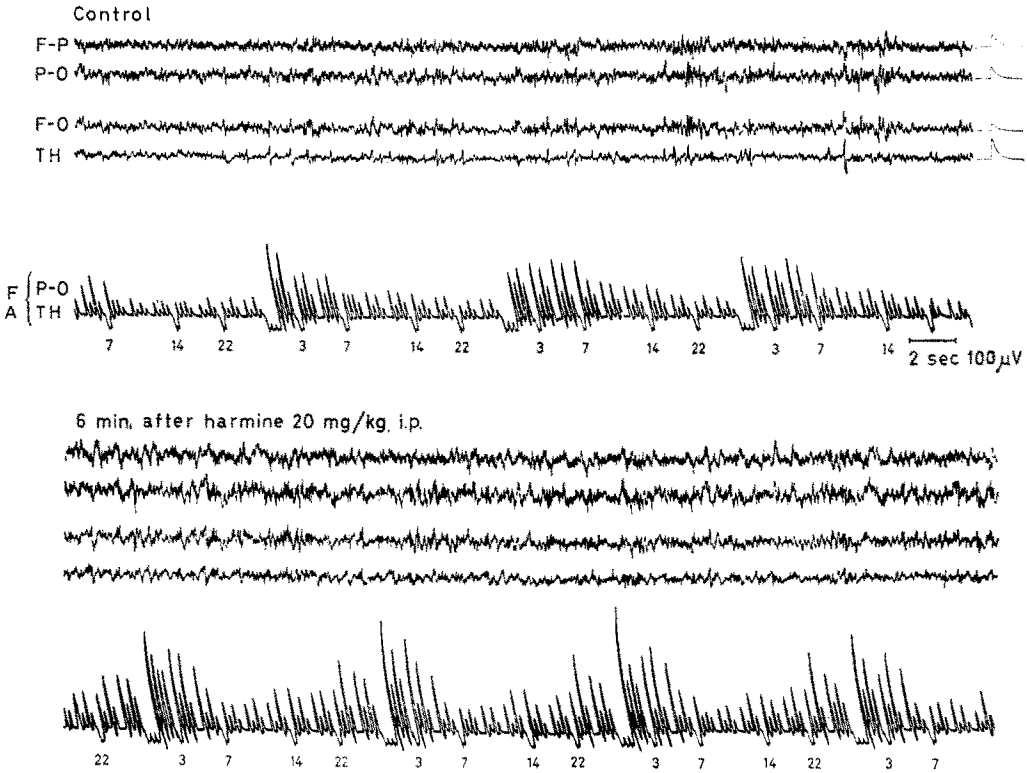


FIG. 1. Effects of harmine on the rat EEG. Tracings registered in a rat with chronically implanted electrodes. An increase in frequency and voltage is noticeable, particularly in the cortical recordings. The frequency analysis of the P–O and TH leads shows an increase of the peaks in the 22–23 c/sec section.

Leads: F–P: fronto–parietal cortex; P–O: parieto–occipital cortex; F–O: fronto–occipital cortex; TH: antero–medial thalamus; FA: Frequency analysis of the P–O and TH leads.

harmine and harmaline (25 mg/kg). 5-HTP did not antagonize the effects of the two alkaloids in the rat, and when injected in doses of 40–50 mg/kg caused the death of the animals.

Harmol, tetrahydro-harmane, 3-methyl-harmane. These three substances gave rise to a toxic syndrome which was clearly different from that observed with harmine and harmaline. Doses ranging from 20–40 mg/kg of harmol caused a brief period of excitement during which the animals exhibited circling movements, and made attempts to grasp their own tails. This was followed by a depressive phase, which had a peculiar character, i.e. the animals spontaneously laid on their bellies, head and tail flat on the floor, remaining in this position for some time (Fig. 2). The animals' eyes were open and they seemed alert. In fact, even slight noises, such as the click of the camera used for photography, aroused them, and the rats then appeared to go about their activities in a normal manner; after a short time they again assumed the above described position. This feature was so typical and constant that it was named the 'harmol position'. L-DOPA, administered in doses of up to 50 mg/kg, did not influence the behavioural patterns provoked by harmol.

The EEG recordings did not show any change which could be considered characteristic of the 'harmol position'. Sometimes the tracing was synchronized; in this case, the EEG

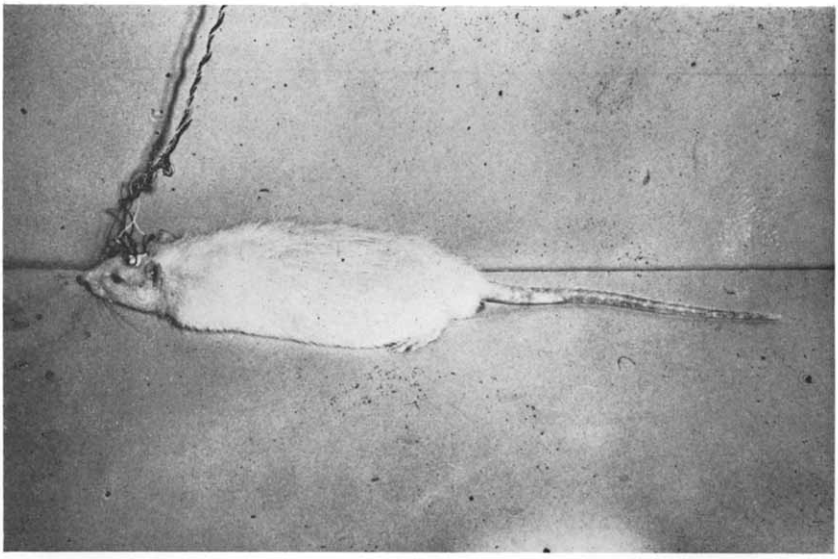


FIG. 2. Typical posture ('harmol position') assumed by a rat treated with harmol (20 mg/kg i.p.). For further explanations see text. The animal is connected to the apparatus for the simultaneous registration of the EEG.

arousal reaction following external stimulation was always present. At other times, even though the animal was lying flat and motionless, the EEG was completely desynchronized.

Tetrahydro-harmane and 3-methyl-harmane, at equivalent dosage levels, caused the same syndrome as observed for harmol.

Harmane and nor-harmane. Harmane and nor-harmane (10 mg/kg) produced a motor depression having a catatonic component. Higher doses (20 mg/kg) led to clonic and tonic–clonic type convulsions; tremors were never observed. After the higher doses, the EEG tracing displayed a typical convulsive pattern, that is, spikes and spikes-and-waves.

II. Rabbit

On the basis of the results obtained in the rat, the effects of harmine, harmaline and harmol were studied in detail in the rabbit.

Previous toxicity tests, performed on animals not bearing electrodes, indicated that the lethal dose of harmaline was 20 mg/kg, while that of harmine was 60 mg/kg. The tremorigenic effect, however, appeared at the same dosage level (2–3 mg/kg) with both substances. With higher doses (5–10 mg/kg) the tremor was accompanied by excitation, ataxia and mydriasis. The frequency of the tremor in the EMG record was 10–12 c/s and displayed a waxing and waning pattern. The effect of harmine lasted longer: after a 5 mg/kg dose of harmine, tremor was present for 10–15 min while with harmaline it did not last more than 5 min. The tremor appeared 30–60 sec after injection and was independent of the spontaneous motor activity displayed by the animal. Later, the tremor was evident only when the animal moved.

The EEG tracings, performed on four animals with chronic electrodes, showed the same increase in frequency and amplitude of the cortical waves as that observed in the rat. Moreover, the hippocampal theta waves (4–5 c/sec) became progressively disorganized and at times were replaced by a low voltage rapid (20 c/sec) activity. With higher doses (10–20 mg/kg) of both drugs, an EEG *grand mal* pattern was occasionally seen.

Six experiments were performed on acutely prepared animals. Three of these were curarized and femoral blood pressure was measured. The EEG findings in these animals were similar to those of the chronically prepared animals; particularly, the increase of frequency and amplitude of the cortical waves observed in the curarized preparations led to the conclusion that this is a phenomenon occurring independently of the augmented muscular activity. Bradycardia and an increase in blood pressure were the other effects observed.

In the rabbit, contrary to that observed in the rat, L-DOPA was effective in antagonizing the tremors and the other toxic symptoms caused by the two drugs. The tremors caused by 5–10 mg/kg of harmine and harmaline were immediately attenuated by the i.v. administration of 5 mg/kg of L-DOPA and usually completely disappeared within 5 min. In Fig. 3, the EMG registration clearly demonstrates this effect; interestingly, the simultaneous EEG recording was not altered significantly. The duration of the effect of a 5 mg/kg dose of L-DOPA was transitory; tremors and other toxic symptoms reappeared, but they could be controlled by additional injections. Higher doses of L-DOPA (20 mg/kg) had a lasting and apparently curative effect, in that all toxic signs disappeared and the animal appeared essentially normal, except for a slight degree of excitation.

Atropine, in doses of up to 5 mg/kg, and 5-hydroxytryptophan, up to 20 mg/kg, were without effect on the toxic syndrome produced by the two alkaloids; on the other hand, pentobarbitone abolished the tremors only at doses (15 mg/kg i.v.) which caused a profound depression of the animal, to the point that the animal lost the righting reflex and lay on its side.

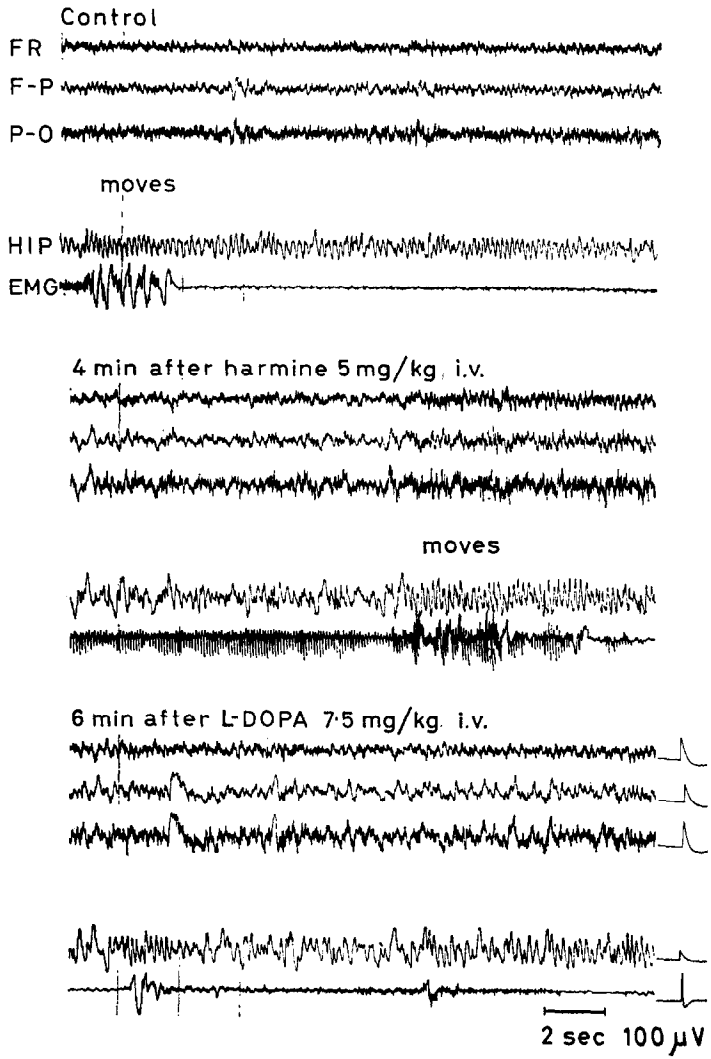


FIG. 3. Antagonistic effect of L-DOPA on harmine tremors in the rabbit. Tracings recorded in an animal bearing chronically implanted electrodes in various cerebral areas, and a bipolar needle-electrode in the hind leg. After harmine (5 mg/kg), the tremor appeared and was accompanied by an increase in frequency and voltage of the cortical waves; the theta rythm in the hippocampus was partially disrupted. Upon administration of L-DOPA, the tremors disappeared but there were only a few changes in the cerebral electrical activity.

Leads: FR: anterior sensorimotor cortex; F–P: anterior–posterior sensorimotor cortex; P–O: anterior sensorimotor–optic cortex; HIP: dorsal hippocampus; EMG: electromyogram of the hind leg.

In the rabbit, harmol, in doses up to 30 mg/kg, did not cause any significant change in behaviour or the EEG; in particular, what has been previously described as the 'harmol position' in the rat was never observed. Doses of 50 mg/kg brought about a state of excitement followed by convulsions, accompanied by the appearance of spikes in the EEG.

DISCUSSION

The results obtained in these experiments will be discussed from two viewpoints. The first concerns the behavioural effects of the various compounds, as related to the modifications of the cerebral electrical activity. The second deals with the antagonistic effect of L-DOPA on the tremors caused by harmine and harmaline.

Previous work done with the β-carboline analogues of harmine gave some indications that distinct pharmacological effects exist within this group. This study, combining both behavioural observations and recording of the EEG, allowed a more precise delineation of the central effects of these compounds. Based on the results obtained, the seven derivatives can be divided into three groups. The first group includes harmine and harmaline, which cause excitation, tremors, and ataxia both in the rat and in the rabbit. This syndrome is in agreement with previously reported data on these and other laboratory animals (mouse, cat, monkey), (BEER, 1939; CHEN and CHEN, 1939). The frequency of tremors in the rabbit is slightly less than that reported for the mouse (15–20 c/sec) by AHMED and TAYLOR (1959) and by HARA and KAWAMORI (1954), but has the same character of 'waxing and waning' described by these authors. In relation to the EEG effect of the two alkaloids, results obtained in the present experiments have confirmed and extended the preliminary observations of HIMWICH *et al.* (1959), in which a 'modified activation' at the cortical and hippocampal levels after harmine administration (5 mg/kg) was described. Based on the present results, the characteristic EEG effect of these two alkaloids is an increase in both frequency and voltage at the cortical and hippocampal levels. Tracings taken from other cerebral areas, that is, the reticular formation and the caudate nucleus, did not show any significant changes. The fact that a drug causes alterations in electrical activity in a particular cerebral area can not be taken to mean that the drug possesses a specific action in that particular area. However, some authors have data suggesting that there is a cortical effect of harmine and harmaline. HARA and KAWAMORI (1954) reported in the mouse the disappearance of the harmine-induced tremors following decortication.

The second group includes harmol, tetrahydro-harmane and 3-methyl-harmane. These drugs induce a completely different toxic effect, consisting of a depressive syndrome, which can extend to complete paralysis in the rat. Gunn described a similar effect in 1935, and he attributed the depressive syndrome to the alcoholic hydroxyl group present in the molecule. However, this syndrome was also noticed, in the present investigation, with tetrahydro-harmane and 3-methyl-harmane, which do not possess the same chemical characteristics. The position assumed by the rat treated with these 3 substances has some unusual features, and does not appear to have any point in common with that observed after other compounds possessing depressive effects, and it is difficult to classify because of this. On the one hand the 'harmol position' indicates a depression of the motor system, but the absence of catatonia, and the presence of the righting reflex speak for the relative integrity of the postural mechanisms. The immediate response to external stimuli suggests that the sensory system is not significantly affected. This is partly confirmed by the EEG recordings which were not altered throughout the toxic period and remained sensitive to the 'activating' effect of external stimulations. GUNN (1935) reported for harmol a depressive action in other laboratory animals (guinea-pig, rabbit) which were not confirmed in this study in the rabbit. In this animal high doses (50 mg/kg) of harmol caused convulsions and tremors.

The third group includes harmane and nor-harmane. The convulsant properties of harmane were reported by SIGG *et al.* (1964); this present study made evident a clear difference between the effects of these compounds from those of harmine and harmaline, based on

both the toxic syndrome and the EEG alterations. Harmane and nor-harmane cause a catatonic state in rats, and the convulsions observed following high doses were of the clonic type, the corresponding EEG being composed of spikes and spike-and-waves.

The finding that L-DOPA antagonizes the tremors and the other toxic symptoms caused by harmine and harmaline might have important implications in regard to classifying the central action of these alkaloids. The effects of harmine have often been linked to an activity on the extrapyramidal system. The rather discouraging clinical application on the therapy of parkinsonism was based on these theoretical considerations (cf. SOURKES, 1964, for references). On the other hand, the tremorigenic action of harmine has been used as a screening devise for drugs possessing antiparkinsonian activity (ZETLER, 1957). With the discovery of the inhibitory effects of harmine on the monoamine oxidase (PLETSCHER *et al.*, 1959) it was thought that their central effects were dependent on this action. It should be noted, however, that other substances having a similar anti-monoamine oxidase effects do not provoke the same toxic syndrome. Therefore, the tremorigenic effect of these alkaloids must be attributed to other actions. Biochemical studies have indicated that harmine causes a slight increase in brain dopamine in the rat (HOLZER and HORNYKIEWICZ, 1959). According to POIRIER *et al.* (1968) levels of dopamine in the cat striatum were not modified 1 hr after treatment with harmaline (10–15 mg/kg); on the other hand, if treatment with harmaline was prolonged (5 mg/kg every 3 hr, for 24 hr) the dopamine content markedly diminished and the homovanillic acid was reduced to very low levels. These authors suggest that harmaline, in adequate doses, has an effect both on the biosynthesis and destruction of dopamine. In other studies on animals (monkeys and cats) with unilateral lesions in the substantia nigra, POIRIER *et al.* (1966) and SOURKES and POIRIER (1966) have described a significant reduction of the striatum dopamine content, which in the monkey was accompanied by extrapyramidal-type disturbances in the controlateral limbs. The administration of L-DOPA, although increasing the cerebral dopamine content, did not modify the motor syndrome caused by the lesion. On the other hand, in these animals, harmine and harmaline caused an intense tremor, appearing in the limbs with the motor deficit. The effect of L-DOPA on the tremors caused by the two alkaloids was not studied by the aforementioned authors.

The results of this study on an antagonistic effect of L-DOPA suggest that an important part of the toxicity of harmine and harmaline is their influence on cerebral dopamine levels. It should be noted that L-DOPA alleviates tremors in the rabbit but not in the rat; preliminary trials carried out in our laboratory demonstrated that the antagonism exists also in the cat. This may be explained by the fact that in the rat much less dopamine is formed upon administration of L-DOPA (BUTCHER and ENGEL, 1969). The role of dopamine in the genesis of the extrapyramidal disturbances in man is well known (cf. HORNYKIEWICZ, 1966). According to this investigator, along with the anatomo-pathological alteration of the substantia nigra and of the striatum found in parkinsonism, there is a reduction in the dopamine content in these areas, which under normal conditions is high. In support of these theories stand the results obtained in clinical use of L-DOPA, which relieves the rigidity and the ataxia (but not the tremors) of parkinsonian patients (SOURKES, 1964). It seems, however, that there is a certain difference between the effects of L-DOPA in human parkinsonism and the effects provoked by brain lesions in the experimental animal, since POIRIER *et al.* (1966 report that L-DOPA was ineffective in antagonizing the extrapyramidal disturbances in monkey with lesions of the substantia nigra. On the other hand, in laboratory animals it has been demonstrated that L-DOPA antagonizes the depressive effects and the other symptoms of motor deficit caused by reserpine (CARLSSON *et al.*, 1957). ROOS and STEG (1964)

report that dopamine is also effective on the tremors caused by this alkaloid in the rat. However, L-DOPA is without effect on the tremors caused by tremorine in the mouse (LEVY and MICHEL-BER, 1964). In conclusion, these results suggest that the tremors induced by harmine and harmaline may be caused by an effect on the extrapyramidal dopaminergic system. The intimate mechanism of this effect remains to be clarified, bearing in mind that at such a highly integrated level one can not dissociate the dopaminergic from other inter-related systems, which certainly play a role in the various manifestations of extrapyramidal pathophysiology.

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